Understanding Glomerular Disease

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Understanding Glomerular Diseases

- Clinical Syndromes
- Morphology
- Pathogenesis

Glomerular Disease

- Primary Glomerular Disease

  Disorders in which the glomeruli are the sole or predominant tissue involved. Usually these diseases are idiopathic.

- Secondary Glomerular Disease

  Glomerular injury is a feature of a systemic disease involving multiple organs or systems.

Syndromes Associated with Glomerular Disease

- Acute Glomerulonephritis
- Rapidly Progressive Glomerulonephritis
- Chronic Glomerulonephritis
- Asymptomatic Urinary Abnormalities
- Nephrotic Syndrome

Acute Glomerulonephritis Symptoms and Signs

- Hematuria (with RBC casts)
- Proteinuria
- Reduction in GFR
- HTN
- Edema with volume overload
- Oliguria

RPGN
Symptoms and Signs

- More insidious onset than acute nephritis
- Rapid and progressive reduction in GFR
- Oliguria
- Hematuria/Proteinuria

Chronic Glomerulonephritis Symptoms and Signs

- Insidious onset
- Slow, progressive loss of GFR
- HTN
- Variable hematuria/proteinuria

Asymptomatic Urinary Abnormalities

- Few or no symptoms (ie: no HTN, edema, or reduction in GFR)
- Recurrent or persistent hematuria with or without proteinuria
- Isolated, non-nephrotic proteinuria

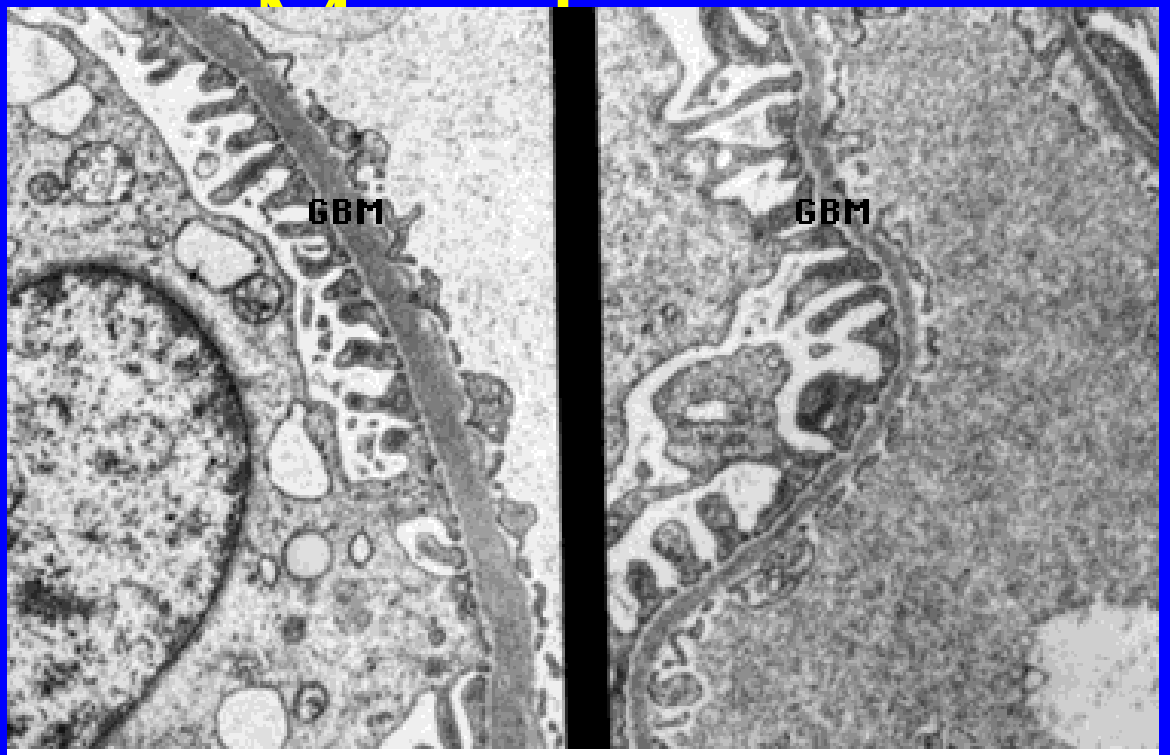
Nephrotic Syndrome Symptoms and Signs

- Proteinuria greater than 3.5 g/day
- Hypoalbuminemia
- Edema
- Lipiduria
- Hyperlipidemia

The Glomerulus

- Capillary network lined by endothelial cells
- A central region of mesangial cells with surrounding matrix, providing support
- The visceral epithelium and associated basement membrane
- The parietal epithelium of Bowman's capsule and basement membrane

Structure of the Glomerular Basement Membrane



Thin basement membrane disease Electron micrograph comparing the thickness of the normal glomerular basement membrane (GBM) (left panel) to the much thinner GBM in thin basement membrane disease (right panel). Courtesy of Helmut Rennke, MD.

Pathogenesis of Glomerular Disease

- Humoral Immune Mechanisms

  -Antibodies reacting with structural or "planted" antigens

  -Circulating immune complexes

  -Soluble mediators (cytokines, complement,

  growth factors, vasoactive hormones)

Pathogenesis of Glomerular Disease

- Cellular Immune Mechanisms

  -T-cell, macrophage, and mononuclear cells

  -Release of cytokines

- Intrinsic Abnormalities of Structure

  -Inherited abnormalities of structural proteins

  (ie, Alport’s syndrome)

Case 1

HPI: 40 y/o white male with 10 year history of persistent microscopic hematuria. Reports 2 episodes of “smoky red” urine in his 20’s, both during URIs. This was accompanied by mild low back pain. Multiple UC’s, cystoscopy x 2, an IVP, and a renal US have all been normal.

Case 1

PMH: Noncontributory.

FH: + Kidney stones in his father.

MEDS: None.

PE: BP 135/80, P65

Otherwise wnl.

Case 1

LABS: S. creatinine 1.0 mg%

UA: 1018, pH 5.0, trace protein, 10-15 RBCs/hpf, no casts, no crystals.

24 hr urine: CI 24 mg/kg/d, TP 225 mg

Urine calcium 125 mg/24 hr

Recurrent or Persistent Hematuria--Differential

- IgA nephropathy
- IgM nephropathy
- Thin-basement membrane nephropathy
- Secondary lesions (Alport's, Fabry's, early SLE, sickle cell disease, sub-clinical PSGN)
- Hypercalciuria/hyperuricosuria
- Urethritis/Vaginitis

IgA Nephropathy Facts

- May present as any of the syndromes discussed in this talk.
- 1-2% of patients/year will come to ESRD.
- Clinical features suggesting a poorer prognosis include: male sex, decreased GFR, HTN, and nephrosis.
- TX for such patients: ACE inhibitors and omega-3 fatty acids.

Case 2

HPI: 33 y/o black male with a 5 year history of proteinuria. In 1989, he had been noted on a routine physical to have 1+ protein. BP and serum creatinine were “normal”. Two years later, he was noted to again have proteinuria. BP was now consistently elevated. Serum creatinine was 1.4 mg%. Now referred with 2 gm protein/24 hrs, serum creatinine 1.7 mg%.

Case 2

PMH: Otherwise unremarkable.

MEDS: Clonidine 0.2 mg tid

PE: BP 165/98, P78, Wght 170 lbs, Hgt 72”

Otherwise unremarkable.

LABS: S. creatinine 1.7 mg%.

UA: 1.012, pH 6.0, 2-3+ protein. 1-2 granular casts. No cells. No fat.

Chronic GN
A Differential

- Primary and Secondary GNs
- Chronic Interstitial Nephritis
- Hypertensive Nephrosclerosis

Some FSGS Facts

- May be primary, or secondary. Most common secondary associations are with HIV disease, heroin use, vesicoureteral reflux, reduced renal mass, sickle cell disease.
- Black patients are at increased risk.
- In nephrotic patients, about 50% renal survival at 10 years.

Case 3

HPI: 24 y/o male presented with 10 day hx of myalgia, fatigue, anorexia, and dark urine. He also noted decreased urine output and lower extremity edema.

PMH: + impetigo 4 weeks earlier, tx'd with topical antibiotics.

ROS: no cough, dyspnea, hemoptysis

Case 3

PE: BP 172/106

Right upper extremity impetiginous lesion, with right axillary adenopathy.

Bilateral lower extremity edema.

LABS: BUN 94mg%, creatinine 9.3 mg%

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Acute Nephritis (An Abbreviated Differential)

- Post-streptococcal GN
- After other viral, bacterial, and parasitic infections
- Mesangiocapillary GN
- Mesangial proliferative GN
- SLE
- Henoch-Schonlein purpura
- Cryglobulinemia (Hepatitis C)
- Infective endocarditis

Acute Nephritis and Reduced Complement Levels

- Reduced
  - -PSGN
  - -Mesangiocapillary GN
  - -Endocarditis
  - -SLE
  - -Cryglobulinemia
  - Atheroembolic disease
- Normal
  - -HSP
  - -IgA Nephropathy
  - -Other Mesangial GNs
  - ANCA GN
  - Anti-GBM GN
  - Immune complex crescentic GN or necrotizing GN

Some PSGN Facts

- Observed after exposure to “nephritogenic” group A (beta-hemolytic) streptococcal infections, either skin or pharyngeal.
- Latent period of about 10 days.
- Often sub-clinical.
- Immune complex mediated (? antigen).
- Largely favorable prognosis, esp. in children.

Case 4

HPI: 56 y/o white female with 10 year hx of of HTN and DM presents for evaluation of proteinuria. 2 years ago had 1+ proteinuria on dipstick; now 4+. Complains of ankle and leg edema over past 6 months. BP has also been poorly controlled over the past 6 months (160/100 range on 4 medications).

Case 4

PMH: "laser surgery" to right eye, 1 year ago. + reflux esophagitis. s/p cholecystectomy.

MEDS: Hydralazine, HCTZ, Atenolol, Clonidine, Glyburide, Ranitidine.

Case 4

PE: BP 168/102, P78

HEENT: Background DM retinopathy on left; laser grid on right.

CV: +S4, no murmur or rub. Right carotid bruit.

Extremities: 2+ pitting edema to knee.

Neuro: Stocking/glove neuropathy bilaterally.

Case 4

LABS: S. creatinine 1.5 mg%, K 5.2 meq/L.

HgbA1C 13.5. LDL 175 mg%.

UA: 1.018, pH 6.0, large glucose, 4+ protein. 0-1 granular cast, oval fat bodies, + free lipid.

RAD: Renal US: No obstruction. Right kidney 12.5 cm; left 12.1 cm.

Nephrotic Syndrome
A Limited Differential

- Primary:

  -Minimal change disease

  -Mesangial proliferative GN

  -FSGS

  -Membranous

  -Membranoproliferative

  -Immunotactoid GN

Nephrotic Syndrome
A Limited Differential

- Secondary:

  -Multisystem/Metabolic disease: Diabetes, SLE, Amyloid, Henoch-Scholein purpura.

  -Drugs: Gold, Penicillamine, Heroin, NSAIDs, Interferon-alpha.

  -Infections: Bacterial and Viral.

  -Neoplasms: Adenoca of lung, colon, stomach, breast, Hodgkin’s disease.

Diabetic Nephropathy Facts

- Leading cause of ESRD in the US.
- Incidence of fixed proteinuria about 30% over 25 years in both NIDDM and IDDM.
- “Typical” DM nephropathy does not require biopsy.
- Aggressive glucose and BP control (with ACE inhibitors) should be pursued.

Case 5

HPI: 55 y/o white female presents with 2 month hx of maxillary sinusitis and hemoptysis. Tx'd for 4 to 6 weeks with serial courses of oral antibiotics/oral steroids. CXR 1 week pta was reported to show a bilateral "pneumonic" process. CBC showed an Hct of 19%. She was referred to WRAMC.

Case 5

PMH: HTN x 15 years. + DM Type II x > 5 years. + COPD (FVC 0.76 L).

ROS: + anorexia with 14 lb wght loss. No fever or chills. + macular/papular rash on ankles 1 week pta.

Case 5

PE: BP 125/65, RR22-26

Macular/papular lesions ankles bilaterally. Lungs with bilateral rales lower fields.

CXR: shown.

LABS: Creatinine 2.3mg%. Hct 19%.

UA: 1.011, pH 6.0, large blood, large glucose. 2+ protein. 2-3 WBC, 30-40 RBC, 3-10 granular casts, occ. RBC casts.

RPGN
An Abbreviated Differential

- Primary Diffuse Crescentic GN
- Superimposed on other Primary GNs
- Associated with infections

  -PSGN, endocarditis, Hepatitis B and C
- Multisystem Diseases

  -SLE, Goodpasture's, HSP, Systemic polyangiitis, cryoglobulinemia
- Medications

Some Wegener's Facts

- Necrotizing granulomatous arteritis of upper and lower respiratory tracts.
- Diffuse or segmental pauci-immune necrotizing GN with crescents.
- Positive cANCA, 90-98% sensitive and specific in patients with a classic presentation.
- Tx: Steroids and cytotoxics.

Oh, gallant was the first love, and glittering and f
The second love was water, in a clear white cup;
The third love was his, and the fourth was mine;
And after that, I always get them all mixed up.

Dorothy Parker